Synthesis of the 13,17 Side Chain Switched Isomers of 18-Hydroxy- and 18-Oxoprogesterone and -deoxycorticosterone[1]

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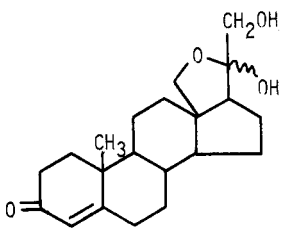
The preparation of the title compounds is described. A model series based on the 18→20 lactone of pregnenolone was prepared by addition of methyl Grignard to form the 18-methyl 18-ketone. Diacetylation, followed by selective hydrolysis at C3 and Oppenauer oxidation gave the enone **10**, the 13,17 side chain switched analogue of 18-hydroxyprogesterone which contains a 2-hydroxyethyl side chain instead of hydroxymethylene. Reaction of the hydroxy ketone derivatives **4**, **6**, and **10** with lead tetraacetate led to very high yields of the acetoxylated enol ethers which could be hydrolyzed by using perchloric acid to the α-acetoxylated ketones. The androstane 18→20 lactone **23** was prepared by using either nitrite photolysis or the hypoiodite reaction. The ketal derived after conversion of **23** to the enone **25** was treated with methyllithium and hydrolyzed to form the 13,17 side chain switched derivative of 18-hydroxyprogesterone. Reaction of **29** with lead tetraacetate formed the acetoxylated enol ether which was hydrolyzed to the α-acetoxylated ketone. Hydrolysis of the acetate yielded the 13,17-switched derivative of 18-hydroxydeoxycorticosterone. Oxidation of the hydroxymethylene groups in **29** and **32** formed the 13,17-switched derivatives of 18-oxoprogesterone and deoxycorticosterone acetate, respectively. Addition of methyllithium to the 3-acetoxy 5-ene lactone produced the 13,17-switched analogue of 18-hydroxypregnenolone which was converted to the α-acetoxylated ketone derivative via the acetoxylated enol ether.

The synthesis of 18-hydroxydeoxycorticosterone (**1**) from conessine was reported by Pappo in 1958.[2] Since **1** has



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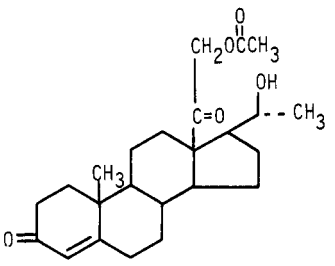

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been shown to be a mineralocorticoid[3] and has been further implicated as a hypertensive agent,[4] a variety of new syntheses of this compound have appeared.[5] Because of our interest in the synthesis and chemical properties of 18-substituted steroids and their potential biological use as antihypertensives, we were interested in preparing analogues and the isomer of **1** where the hydroxymethylene at C13 and the hydroxyacetyl side chain of C17 have been exchanged. As a model for the preparation of the desired switched compounds, the lactone **3** was to be converted into the 13,17-switched analogue of 18-hydroxydeoxycorticosterone acetate. The resultant initial synthetic objective **2** would thus possess an additional methyl group at C20.

The synthetic sequence called for condensing the 18→20 lactone **3**, a compound which is easily accessible from pregnenolone acetate in three steps,[6] with methyl Grignard (Scheme I). This reaction has been described and the steroid shown to undergo addition of a single equivalent of Grignard.[7] For facilitation of chromatographic separation, the diol **4** was acetylated to a mixture of the mono- and diacetates **6** and **5**. However, when the acetylation mixture was separated on silica, the enol ether **7** was formed in 70% yield at the expense of the monoacetate **6**. Treatment of **7** with aqueous *p*-toluenesulfonic acid slowly regenerated **6**, thereby confirming the structure of **7** as an enol ether.[7,8]

Selective hydrolysis of the 3β-acetate in **5** was achieved by reaction of **5** with sodium carbonate for a short period of time to yield **8** in 97% yield. The conversion of the 3-hydroxy 5-ene grouping in **8** into the conjugated enone could be accomplished, in 74% yield, by using standard Oppenauer conditions[9] or in better yield (84%) by using *N*-methyl-4-piperidone in place of cyclohexanone according to Watt's procedure.[10] In addition to the newly formed enone absorptions at 1685 and 1625 cm^{-1} in **9**, the infrared spectrum clearly showed the C20-acetate at 1735 cm^{-1} and the C18-ketone at 1700 cm^{-1}. Cleavage of the C20-acetate in **9** was easily accomplished with potassium carbonate in methanol to yield the hydroxy ketone **10** in 97% yield. Compound **10** is an analogue of 18-hydroxyprogesterone where the C13 and C17 side chains have been exchanged.[11]

In order to convert the C13-acetyl side chain into the corticoid side chain, it was necessary to introduce an acetoxy group on the 18-methyl group. Kirk has shown

(1) Preliminary communication: Lenz, G. R. *J. Chem. Soc., Chem. Commun.* **1978**, 241.
(2) Pappo, R. *J. Am. Chem. Soc.* **1959**, *81*, 1010.
(3) Gotshall, R. W.; Davis, J. O. *Am. J. Physiol.* **1973**, *224*, 1116.
(4) (a) Melby, J. C.; Dale, S. L.; Grekin, R. J.; Gaunt, R.; Wilson, T. E. *Recent Prog. Horm. Res.* **1972**, *28*, 287. (b) Edelman, I. S.; Fanestil, D. D. In "Biochemical Actions of Hormones"; Litack, G., Ed.; Academic Press: New York, 1970; Vol. 1, p 321. (c) Oliver, J. T.; Birmingham, M. K.; Bartova, A.; Li, M. P.; Chan, T. H. *Science (Washington, D.C.)* **1973**, *182*, 1249.
(5) (a) Kirk, D. N.; Ragjagopalan, M. S. *J. Chem. Soc., Chem. Commun.* **1974**, 145. (b) Kirk, D. N.; Rajagopalan, M. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1860. (c) Bolliaz, M.; Kalvoda, J.; Schmidlin, J. *Helv. Chim Acta* **1975**, *58*, 1425. (d) Li, M. P.; Lantos, C. P.; Traikov, H.; Birmingham, M. K.; Chan, T. H. *J. Steroid Biochem.* **1970**, *1*, 259. (e) Li, M. P.; Birmingham, M. K.; Chan, T. H. *J. Org. Chem.* **1976**, *41*, 2552. (f) Slaunwhite, W. D.; Solo, A. J. *J. Pharm. Sci.* **1975**, *64*, 168 (for conflicting results in the Oppenauer oxidation of an 18,20-diol, see, however: Eignerova, L.; Kasal, A., *Collect. Czech. Chem. Commun.* **1976**, *41*, 1056). (g) Lenz, G. R. *J. Org. Chem.* **1976**, *41*, 3532.
(6) Heusler, K.; Wieland, P.; Meystre, C. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V., p 692.
(7) Baddeley, G. V.; Carpio, H.; Edwards, J. A. *J. Org. Chem.* **1966**, *31*, 1026.
(8) Enol ethers have been observed in this system under forcing conditions: tosyl acid in refluxing benzene[7] or pyrolysis (Cerný, V.; Kasal, A.; Sorm, F. *Collect. Czech. Chem. Commun.* **1966**, *35*, 1752).
(9) Djerassi, C. *Org. React.* **1951**, *6*, 207.
(10) Raggio, M. L.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 1873.
(11) For a discussion of the preferred conformation of the 18-acetyl group in 18-norpregnenes, see ref 7.

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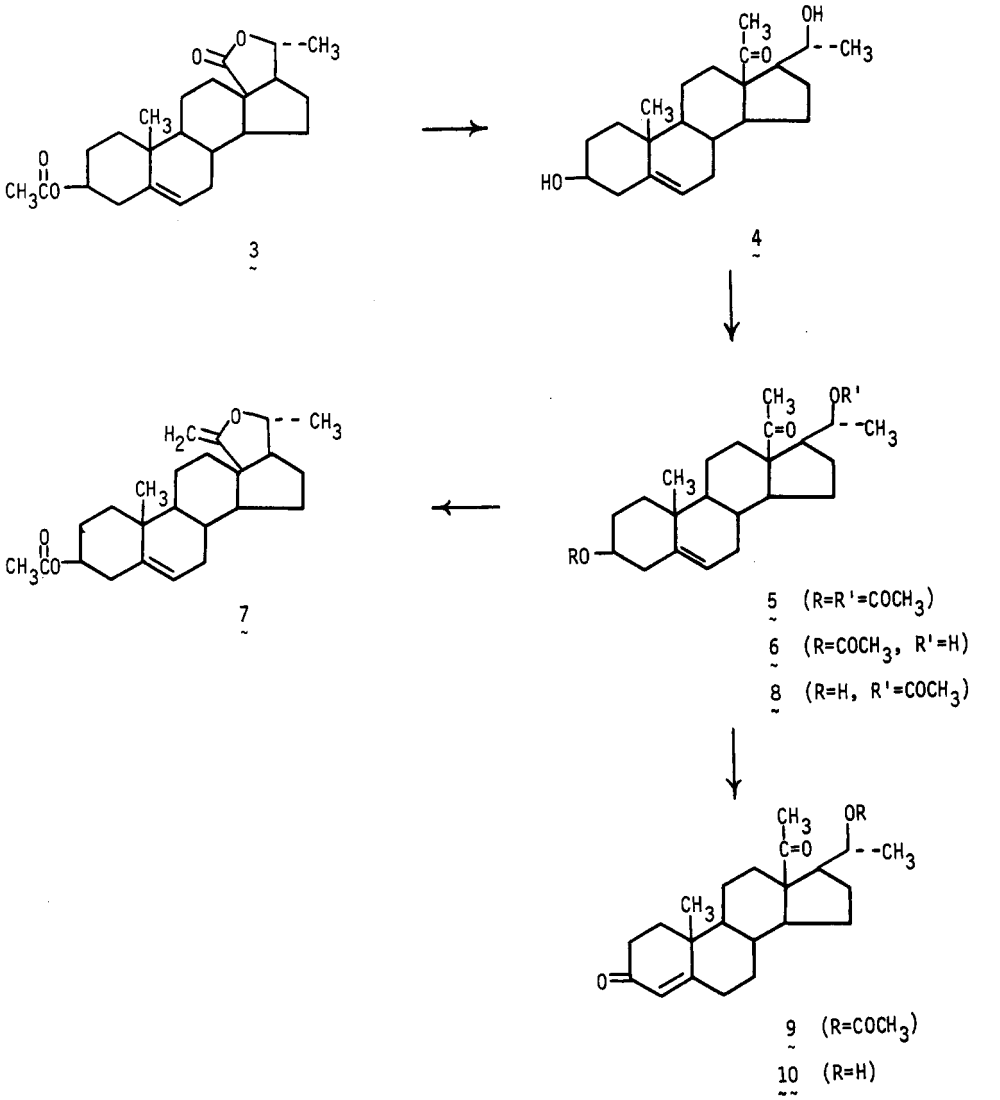
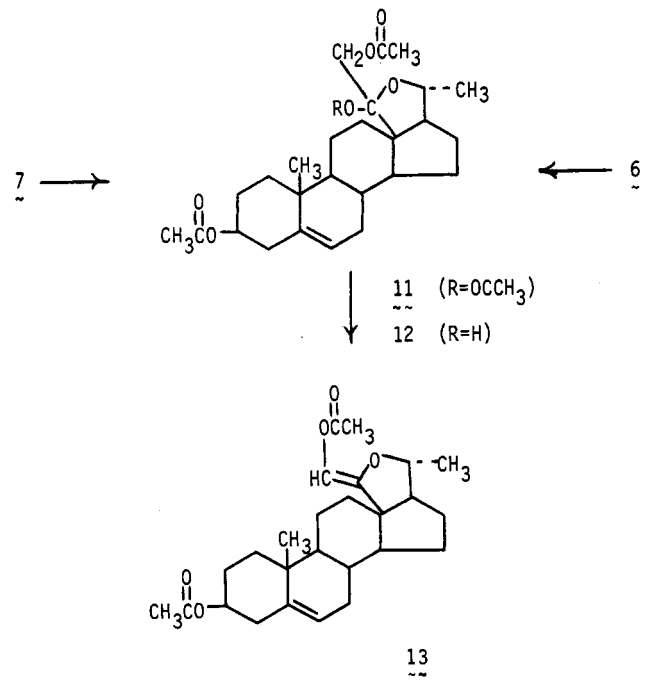
Scheme I

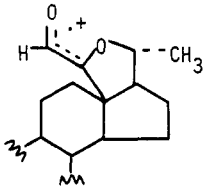


Scheme II



that the hemiketal of 18-hydroxyprogesterone is efficiently converted into 18-hydroxydeoxycorticosterone acetate by lead tetraacetate in acetic acid and has postulated the intermediacy of an enol ether as the reactive species on the basis of specific deuteration studies.[5a,b] This hypothesis was proven when Swiss workers found that the 18-hydroxy 20-ketone hemiketal could be dehydrated to the postulated enol ether in high yield by using aluminum isopropoxide in refluxing toluene and subsequently acetoxylated by using Kirk's conditions.[5c] Although the hydroxy ketone function in 20β-hydroxy-18-methyl 18-ones does not exist as the hemiketal, as does 18-hydroxyprogesterone, the facile formation of the enol ether 7 with silica indicated that this reaction might be successfully applied to these hydroxy ketones. When the enol ether 7 was reacted with lead tetraacetate in acetic acid, a single product was formed in 90% yield. Treatment of the hydroxy ketone 6 furnished the same compound in 92% yield (Scheme II). This product, however, was not the expected α-acetoxy ketone 12 but possessed very distinctive spectral features which led to its identification as the stereospecifically formed *Z* enol ether 13 of the desired product. The elemental analysis indicated the loss of 1 mol of water from the expected 12, and the mass spectrum confirmed this with a molecular ion at *m/e* 428. The NMR spectrum of 13 was particularly instructive. In addition to showing two separate acetyl methyl groups, a very sharp one proton singlet occurred at δ 6.70 for the vinylic hydrogen of the enol ether. Because of the rigidity of the hydrofuran ring in 13, the C20 hydrogen forms a 90° dihedral angle with

the C17 hydrogen and appears as a sharp quartet at δ 4.36 due to coupling only with the C21 hydrogens.[12] The infrared spectrum indicated two different types of acetate groups with absorptions at 1740 and 1730 cm^{-1} and a weak enol ether band 1685 cm^{-1}. The dioxygenated double bond in **13** gives rise to strong $\pi\pi^*$ ultraviolet absorption at 224 nm (ϵ 7500). The mass spectrum was also useful in assigning the structure to 13. Besides a weak parent, a major peak (99.5%) corresponds to the loss of acetyl from the enol of **13**, while the base peak corresponds to the loss of this acetyl and the 3β-acetoxy group. Cleavage of the acetyl group of the enol ether would be expected to be very favorable due to the formation of a stable oxallylic radical cation (**14**), while cleavage of the acetoxy group would form



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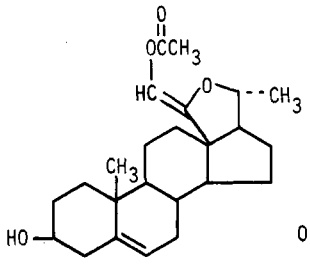
an unfavorable vinyl radical cation. On this basis and further chemical transformations on members of this series, the enol ether structure indicated in **13** was assigned. The assignment of the stereochemistry of **13** as *Z* was based on inspection of models of the *E* and *Z* isomers. While the *Z* isomer is sterically unencumbered, it is impossible to find a rotamer of the acetyl group in the *E* isomer which does not experience severe steric interactions with one or more of the axial C-6, C-8, or C-11 hydrogens and especially the angular methyl group.

Treatment of the 3β-hydroxy analogue of **4** with lead tetraacetate gave the 3β-hydroxy derivative **15** in 77%



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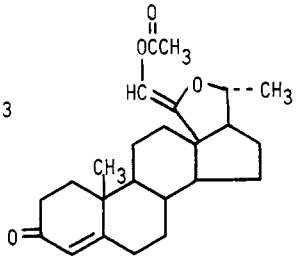

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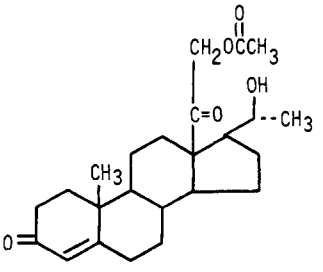

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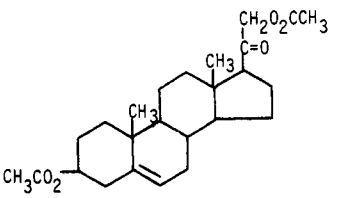
yield. Similar treatment of the enone **10** furnished the enol ether **16** in 82% yield. Both acidic and basic hydrolyses of **16** to give **2** were considered. Basic hydrolysis was rejected since hydrolysis of the acetate would probably lead

Chart I



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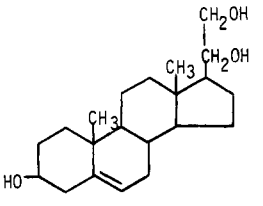

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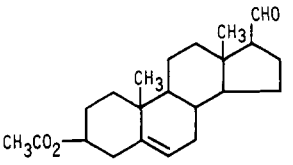

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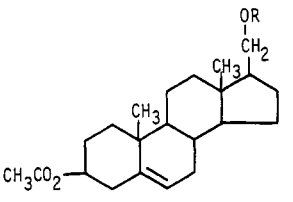
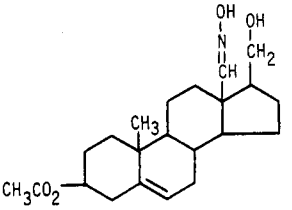


20 (R=H)

21 (R=NO)



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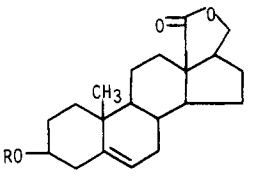


23 (R=CH_3CO)

24 (R=H)

to an 18-aldehyde after protonation. Acidic hydrolysis of **16** could also lead to an 18-aldehyde or to the desired **2**, depending on which vinylic carbon was protonated. On the basis of a comparison of the electron-donating abilities of an acetoxyl vs. a methoxyl substituent and also of the fact that protonation of the acetoxyl vinylic carbon would form a tertiary carbonium ion as opposed to a secondary carbonium ion, if the other vinylic carbon were protonated, acidic hydrolysis should lead to the desired product **2**. When **16** was treated with aqueous *p*-toluenesulfonic acid under conditions which hydrolyzed the unsubstituted enol ether **7**, it was recovered unchanged after 7 h of reaction. Since both **16** and **2** contain a variety of sensitive groups, it was necessary to find a mild fast method for hydrolysis. The method selected was that developed by Wettstein for the hydrolysis of 21-deoxyaldosterone 3,20-bisketal.[13] Treatment of **16** with 2.8 M perchloric acid in tetrahydrofuran for 5 min and a subsequent workup yielded the desired **2** in 80% yield. Compound **2**, the analogue of 18-hydroxydeoxycorticosterone acetate (**1**), was characterized by infrared absorptions for a hydroxyl at 3440 cm^{-1}, an acetate at 1755 cm^{-1}, and the 18-ketone at 1715 cm^{-1}. In the NMR spectrum, the olefinic proton of the enol ether had disappeared and was replaced by an AB quartet for the geminal protons of the 18-methylene group.

Since we were successful in the model series in exchanging the C13 and C17 side chains, we next turned our attention to the parent series. The critical compound in this series was the lactone **23** (Chart I), an unknown compound. The envisaged precursor to this molecule was the alcohol **20**. This alcohol was prepared from 21-acetoxypregnenolone[14] (**17**) by lithium aluminum hydride reduc-

(12) (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11. (b) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

(13) Schmidlin, J.; Wettstein, A. *Helv. Chim. Acta* **1963**, *46*, 2799.

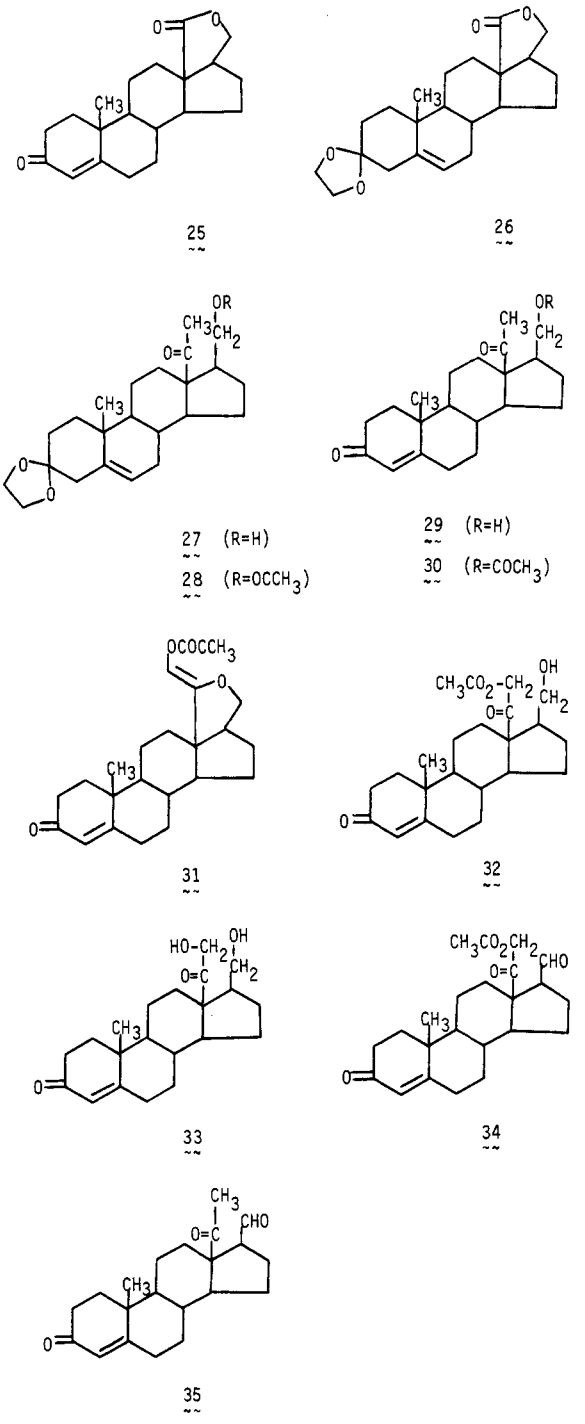
(14) Steiger, M. and Reichstein. T., *Helv. Chim. Acta* **1937**, *20*, 1164.

tion to the triols 18,[15] which were, in turn, cleaved by sodium periodate to give the aldehyde **19** after acetylation of the 3β-alcohol.[16] This series of reactions has been described in analogous series.[17] The aldehyde group in **19** was reduced with lithium tri-*tert*-butoxyaluminum hydride to the primary alcohol forming **20**[18] in good overall yield. Reduction of **19** with sodium borohydride resulted in significant cleavage of the 3β-acetate to the 3β-alcohol, a compound which was useless for our purposes since it was not possible to selectively reacetylate to form **20**.

Two approaches were considered for the remote functionalization of the angular C13-methyl group in alcohol **20**: (a) nitrite photolysis (the Barton reaction)[19] and (b) the hypoiodite reaction.[20] There is a paucity of information about the results of either reaction on primary C20-alcohols. The nitrite ester **21** was quantitatively prepared from **20** with nitrosyl chloride in pyridine and was characterized by TLC and NMR. Irradiation formed minor amounts of aldehyde **19** and alcohol **20**, and the major product, the oxime **22**, was isolated in 26% yield after chromatography. Jones oxidation[21] of the oxime **22** furnished the desired lactone **23** in 49% yield.[22,23] The overall yield of 13% of **23** from alcohol **20** was not considered sufficiently high to be useful for the planned synthetic sequence. The yield of lactone **23** improved significantly to between 44% and 51% when the hypoiodite reaction was run on alcohol **20**. This is perhaps not surprising since in the Barton reaction the alkoxy radical is only formed once when the nitrogen–oxygen bond in the nitrite fragments. On the other hand, the alkoxy radical can be formed from lead tetraacetate and iodine many times during the reaction, thus enhancing the probability for hydrogen abstraction from the C13-methyl group.

At this point it was necessary to convert the 18→20 lactone into an acetyl group at C13 and a hydroxymethylene group at C17β. While Grignard addition analogous to the conversion of **3** to **4** would work, the fact that the C20-alcohol would be primary rather than secondary as in **4** rendered the success of the bis-acetylation and selective hydrolysis sequence used in the model series unlikely. Alternatively, a ketal-protected enone would be unlikely to survive refluxing with methyl Grignard for several days in toluene. As a result, the addition of methyllithium to the lactone to form the desired functionality was investigated. The addition of methyllithium to hindered lactones has been studied by Fetizon in the triterpene series.[24] The 3β-acetate in **23** was cleaved with sodium methoxide, and the resulting alcohol **24** was oxidized to the enone **25** (Chart II) by using the modified Oppenauer reaction in 73% overall yield.[10] The Δ^5-3-ketal **26** was formed by using the ethylene glycol vacuum distillation method[25] and subjected to the action of methyllithium in ether to yield the ketal of the desired 13,17-switched isomer of 18-hydroxyprogesterone (**27**) in 73% yield. Hydrolysis using *p*-toluenesulfonic acid in acetone, containing water to prevent enol ether formation, gave one of the target compounds, **29**, the 13,17-switched isomer of 18-hydroxyprogesterone, in 97% yield. Like the model **10**, compound **29** also exists exclusively in the open hydroxy ketone form as indicated by a strong carbonyl absorption in the IR and an acetyl methyl group resonance in the NMR. Further chemical evidence for the hydroxy ketone was obtained by acetylation of the hydroxyl group at room temperature for a short time to yield the acetate **30**. Alternatively, **30** could be obtained via acetylation of the

Chart II

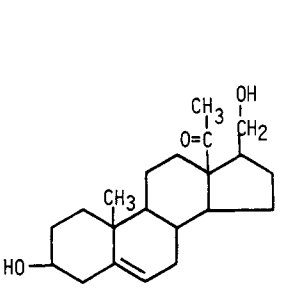


(15) Steiger, M. and Reichstein, T., *Helv. Chim. Acta* **1938**, *21*, 171.
(16) (a) Miescher, K.; Hunziker, F.; Wettstein, A. *Helv. Chim. Acta* **1940**, *23*, 400. (b) *Ibid.* **1940**, *23*, 1367.
(17) (a) Gelbart, A.; Thomas, R. *J. Med. Chem.* **1978**, *21*, 284. (b) Gelbart, A.; Boutagy, J.; Thomas, R. *Ibid.* **1979**, *22*, 287.
(18) Compound **20** has not been described in the literature but was claimed in a patent by: Ruzicka, L.; Prelog, V. U.S. Patent 2 509 171; *Chem. Abstr.* **1950**, *44*, 7864a.
(19) Hesse, R. H. *Adv. Free-Radical Chem.* **1969**, *3*, 83.
(20) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.
(21) Bowdon, K.; Heilbronn, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.
(22) The oxidation of oximes with neighboring alcohols to form lactones is a general reaction. See: Barton, D. H. R.; Beaton, J. M.; Gellen, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 4076.
(23) It is interesting to note that the NMR spectrum of the lactone **23** the C20 hydrogens are geminally split, but only the 20α-hydrogen is coupled to the C17α-hydrogen since the 20β-hydrogen forms a 90° dihedral angle, identical with that observed in enol ether **13**.
(24) Borg, S.; Fetizon, M.; Rens, J. *Bull. Soc. Chim. Fr.* **1966**, 2011.
(25) Allen, W. S.; Bernstein, S.; Littell, R. *J. Am. Chem. Soc.* **1959**, *76*, 6116.

ketal **27**, forming **28**, and subsequent deketalization. Acetylation of the 18-hydroxyl in 18,20-hemiketals is known to occur in low yields by refluxing it overnight in acetic anhydride–pyridine mixtures.[26] Introduction of the acetoxy group α to the 18-ketone in **29** was accomplished in a manner analogous to that for the model series by using lead tetraacetate in acetic acid and generated the acetoxylated enol ether **31** in 92% isolated yield.[27] Specific hydrolysis of the acetoxylated enol ether by using Wettstein's perchloric acid method yielded the α-acetoxylated ketone **32**.[13] Hydrolysis of the acetate group in **32** was accomplished in 54% yield by using potassium bicarbonate which is described by von Euw as specific for α-acetoxy ketones.[28] The compound thus generated, **33**, is the 13,17-switched isomer of 18-hydroxydeoxycorticosterone (**1**). The major objective of this work was thus accomplished.

Since both the 13,17-switched isomers of 18-hydroxyprogesterone and 18-hydroxydeoxycorticosterone, **29** and **32**, respectively, exist in the open hydroxy ketone form, we were interested in preparing the aldehydes from the hydroxymethylene group at C17. 18-Oxodeoxycorticosterone was considered for many years to be the "unknown" mineralocorticoid responsible for causing hypertension and was recently synthesized by Kalvoda and co-workers.[29] On the other hand, 18-oxoprogesterone was originally synthesized by Pappo[2] and by Wettstein[30] many years ago. Although the thermodynamic equilibrium favors the 17β configuration of the acetyl side in progesterone over the 17α by seven to three,[31] the introduction of oxygen at C18 strongly shifts this equilibrium in favor of the 17α isomer.[32] The exceptions to these observations are 18-hydroxy derivatives of progesterone and deoxycorticosterone which exist completely in the hemiketal form and are thus effectively frozen in the 17β configuration. Compound **32** was oxidized to the aldehyde by using buffered pyridinium chlorochromate[33] in order to avoid epimerizing conditions. This reagent cleanly gave the aldehyde **34** in 50% yield as indicated by a single doublet for the aldehydic hydrogen at δ 9.72 in its NMR spectrum. On the other hand, similar oxidation of the switched progesterone derivative **29** formed the 13,17-switched derivative **35** of 18-oxoprogesterone which was contaminated by approximately 10% of the 17α isomer. The presence of this epimer was indicated by an additional upfield doublet for the aldehydic hydrogen and a singlet for the acetyl methyl group. Recrystallization removed the 17α epimer and furnished pure **35**, 13,17-switched 18-oxoprogesterone.

Returning to the initial 18→20-lactone **23**, the 3β-hydroxy-5-ene 13,17-switched derivatives were prepared by treatment of **23** with methyllithium to produce the 13,17-switched derivative **36** of 18-hydroxypregnenolone.



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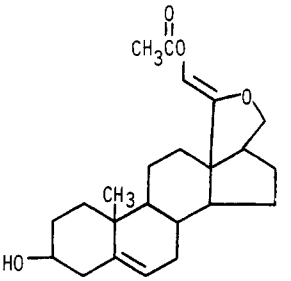

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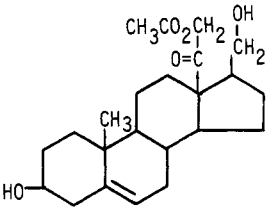

38

Reaction of **36** with lead tetraacetate in acetic acid formed the acetoxylated enol ether **37** which was hydrolyzed to the 13,17-switched analogue **38** of 18,21-dihydroxypregnenolone 21-acetate.

The reason for the facile formation of enol ethers in the 20-hydroxy 18-ketone steroids is steric in nature and becomes apparent when a molecular model is considered. Although the hydroxy ketones do not exist as hemiketals, a model indicates that the two functional groups are perfectly arranged for addition of the hydroxyl group across the carbonyl group. However, a model of either the *R* or *S* isomer of the resultant hemiketal demonstrates severe steric interactions between the 18-methyl group and the angular 10-methyl as well as the axial hydrogens at C-8, C-11, and C-15. This results because the hemiketal formation occurs endocyclic to the steroid as opposed to 18-hydroxyprogesterone where hemiketal formation occurs away from the steroid. The steric interactions in the hydroxy ketone are either eliminated or much diminished when the 18-methyl group is attached to a trigonal carbonyl moiety when compared to a tetrahedral carbon atom in the hemiketal. However, when the 18-ketone is polarized by either protonation or complexation with a Lewis acid, hemiketal formation occurs, followed by spontaneous elimination of water to form the enol ether. This was seen in treatment of the hydroxy ketone **6** with silica and must occur with acetic acid in the lead tetraacetate acetoxylation since both the hydroxy ketone **6** and its enol ether **7** yield the same acetoxylated enol ether **13** in virtually identical yields. It is interesting to note that after reaction of **7** with lead tetraacetate, it presumably exists as **11** which is the acetate of the hemiketal. If the enol ether **13** were formed directly in the reaction, it would reasonably be expected to be more reactive than the starting enol ether **7** and would undergo further reaction with the lead tetracetate. Upon workup, **11** spontaneously eliminates acetic acid to form the acetoxylated enol ether **13**.

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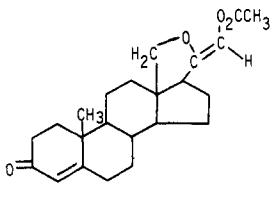
(27) The same type of compound is formed (A, mp 155 °C ded) when the 21-acetate of **1** was treated with dimethyl sulfoxide and acetic anhydride. The same stereochemistry is assigned on the basis of identical UV maxima and intensities for A, **16**, and **31**. The mass spectral fragmentation pattern of A is identical with that of **13** and **16** while the proton geminal to the acetoxyl group resonates at δ 6.52.



A

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(31) Butenandt, A.; Schmidt-Thomé, J.; Paul, H. *Ber.* **1939**, *172*, 1112.

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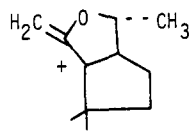
Experimental Section

General Methods. Melting points were run on a Thomas-Hooever Unimelt capillary apparatus and are uncorrected. IR spectra were recorded in potassium bromide on a Beckman IR-12, and ultraviolet spectra were run in methanol on a Beckman DK-2a spectrophotometer. NMR spectra were recorded on a Varian A-60, FT-80, or XL-100 spectrometer and were run in deuteriochloroform with tetramethylsilane as an internal standard, unless otherwise noted. The NMR spectra are reported in chemical shifts (δ), followed by a first-order analysis of the splitting pattern: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The multiplicity is followed by the coupling constant in hertz where appropriate and then the integrated signal intensity. Optical rotations were measured in chloroform on a Perkin-Elmer 141 polarimeter. Microanalyses were determined by the Searle Laboratories Microanalytical Service under the direction of Mr. Emmanuel Zielinski.

Reaction of 3β,20β-Dihydroxypregn-5-en-18-oic Acid 18→20-Lactone 3-Acetate (3) with Methylmagnesium Chloride. To a solution of 10.0 g of **3** in 500 mL of dry toluene was slowly added 275 mL of 2.9 M methylmagnesium chloride in THF, and the mixture refluxed for 74.5 h. After cooling, the contents of the flask were poured onto ice, and the flask was rinsed with toluene and then ethyl acetate. The aqueous layer was acidified with concentrated hydrochloric acid and chloroform added until all the solids dissolved. The aqueous layer was separated, and the organics were washed with dilute sodium bicarbonate solution. After the mixture was dried with sodium sulfate, the solvents were removed, and the residue was acetylated for 66 h with 40 mL of acetic anhydride and 50 mL of pyridine. After the acetylating mixture was poured onto ice and 250 mL of chloroform added, the aqueous layer was separated and the organic layer washed twice with water and once with dilute hydrochloric acid. The chloroform layer was dried with sodium sulfate. TLC on silica indicated the presence of two compounds (1:4 and 1:9 ethyl acetate–benzene). After the solvent was removed under reduced pressure, the residue was submitted to low-pressure liquid chromatography on a column of Woelm silica (1 × 36 in.), and 25 mL fractions were taken. TLC examination indicated the presence of two minor and one major component while the more polar of the two initial compounds was much diminished in size on the TLC plate. Fractions 22–30 (1:9 ethyl acetate–benzene) yielded 651 mg of 5′,17α-dihydro-5′α-methyl-2′-methylene-2′*H*-18-nor-17α-androst-5-eno[13,17-*c*]furan-3β-ol acetate (**7**): mp 139–141.5 °C (acetone–water); IR 1735 cm^{-1}; NMR δ 5.42 (m, 1 H, C6 H), 4.58 (vbr m, 1 H, C3α H), 4.35 (d, J = 1.5 Hz, 1 H, vinyl H), 4.17 (q, J = 13, 7 Hz, 1 H, C20β H), 3.85 (d, J = 1.5 Hz, 1 H, vinyl H), 2.00 (s, 3 H), 1.25 (d, J = 7 Hz, 3 H, C21 H), 1.05 (s, 3 H, C19 H); MS, *m/e* (relative intensity) 370 (parent, 22), 355 (CH_3, 13), 310 (CH_3CO_2H, 62), 295 (CH_3, $C_2H_4O_2$, 45), 137 (I, 77). Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.54, 77.98; H, 9.19, 9.11.



I

Elution was continued until fraction 65 with 1:9 ethyl acetate–benzene, when it was changed to a 1:19 ratio, and the fractions were collected overnight. Fractions 51–95 yielded 4.30 g of 13β-acetyl-18-norpregn-5-ene-3β,20β-diol diacetate (**5**): mp 138–140 °C (ether–petroleum ether); IR 1745, 1705 cm^{-1}; NMR δ 5.37 (m, 1 H, C6 H); 4.58 (m, 2 H, C3α,20 H) 2.07 (s, 6 H), 2.02 (s, 3 H), 1.18 (d, J = 6 Hz, 3 H, C21 H), 0.90 (s, 3 H, C19 H). Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.75; H, 8.78.

Fractions 155–220 yielded 262 mg of 13β-acetyl-18-norpregn-5-ene-3β,20β-diol 3-acetate (**6**): mp 137.5–140 °C (THF–water); IR 3540 1735 (sh), 1720, 1695 cm^{-1}; NMR δ 5.40 (br s, 1 H, C6 H), 4.58 (br s, 1 H, C3 H), 3.45 (br s, 1 H, C20 H), 2.92 (br m, 1 H), 2.33 (s, 3 H, C18 CH_3), 2.02 (s, 3 H, C3-acetate CH_3), 1.17 (d, J = 6 Hz, 3 H, C21 H), 0.93 (s, 3 H, C19 H); MS, *m/e* (relative intensity) 388 (no parent observed), 370 (–H_2O, 7.1), 310 (–H_2O, –$C_2H_4O_2$, 60), 267 (–$C_2H_4O_2$, –C_2H_3O, 51), 43 (C_2H_3O, 100). Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.33; H, 9.42.

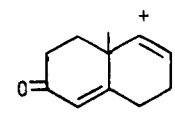
13β-Acetyl-18-norpregn-5-ene-3β,20β-diol (4). A solution of 0.976 g of **5** in 75 mL of methanol was stirred vigorously and 2 g of potassium carbonate added. After 30 h, an additional 1 g of potassium carbonate was added. After an additional 16 h, 500 mL of distilled water was added, and the resultant precipitate was filtered and washed with distilled water until neutral to give 768 mg (2.22 mmol, 98%) of **4**: mp 177–179 °C; IR 3450, 1695, cm^{-1}; NMR δ (Me_2SO-d_6) 5.25 (m, 1 H, C6 H), 4.48 (m, 2 H, C3,20 H), 2.23 (s, 3 H, C18 CH_3), 1.02 (d, J = 6 Hz, 3 H), 0.80 (s, 3 H, C19 H). Anal. Calcd for $C_{22}H_{34}O_3$·0.5H_2O: C, 74.32; H, 9.92. Found: C, 73.89; H, 9.51.

13β-Acetyl-18-norpregn-5-ene-3β,20β-diol 20-Acetate (8). A solution of 1.026 g (2.39 mmol) of **5** in 75 mL of methanol was stirred magnetically, and 2 g of potassium carbonate in 10 mL of distilled water added. After 1.25 h, TLC indicated complete conversion to the monoacetate, 425 mL of distilled water was added, and the white precipitate was filtered and dried to give **8**: 899 mg (2.32 mmol, 97%); mp 201–203 °C; IR 3550, 1735, 1695 cm^{-1}; NMR δ 5.33 (m, 1 H, C6 H), 4.60 (m, 1 H, C20 H), 3.47 (m, 1 H, C3 H), 2.70 (m, 1 H), 2.07 (s, 6 H), 1.18 (d, J = 6 Hz, 3 H), 0.88 (s, 3 H, C19 H). Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.04; H, 9.08.

13β-Acetyl-20β-hydroxy-18-norpregn-4-en-3-one Acetate (9). Method A. A 718-mg (1.85 mmol) sample of **8** was dissolved in 125 mL of toluene and 10 mL of cyclohexanone and brought to reflux, and 25 mL was removed via a Dean–Stark trap. Aluminum isopropoxide (2 g) was added and the mixture refluxed for 2 h. After the mixture cooled, 100 mL of saturated Rochelle salt solution was added and the mixture steam distilled until no more organics were condensed in the receiver. When the solution was cooled, a solid appeared which was filtered, dissolved in methylene chloride, dried with sodium sulfate, and diluted with ethyl acetate. After condensation to a small volume, the solution was diluted with petroleum ether and, after standing, 461 mg of **9** was filtered off. Evaporation to dryness and addition of ether gave a second crop of 69 mg (total 530 mg, 1.37 mmol, 47%) of **9**.

Method B. A mixture of 1.65 g (4.25 mmol) of **8**, 150 mL of toluene, 5 mL of 4-piperidone, and 2 g of aluminum isopropoxide was refluxed for 3 h. After cooling, the solution was washed twice with dilute hydrochloric acid, and the toluene solution was dried with sodium sulfate and evaporated. Crystallization from ether–petroleum ether gave **9**: 1.38 g (3.57 mmol, 84%); mp 180–182 °C; IR 1735, 1700, 1685, 1625 cm^{-1}; UV 240 nm (ϵ 16 000); NMR δ 5.73 (s, 1 H, C4 H), 4.63 (br m, 1 H, C20 H), 2.10 (s, 3 H), 2.08 (s, 3 H), 1.28 (d, J = 5.5 Hz, 3 H), 1.08 (s, 3 H, C19 H). Anal. Calcd for $C_{24}H_{34}O_3$: C, 74.57; H, 8.87. Found: C, 74.41; H, 8.82.

13β-Acetyl-20β-hydroxy-18-norpregn-4-en-3-one (10). To a solution of 1.374 g (3.55 mmol) of **9** in 100 mL of methanol was added 4 g of potassium carbonate dissolved in 15 mL of distilled water. After the mixture was stirred under nitrogen for 20 h, the volume was brought to 500 mL by the addition of distilled water and the methanol removed on a rotary evaporator under reduced pressure. The resultant **10** was filtered and dried: 1.182 g (3.43 mmol, 97%); mp 160–164.5 °C. Since it was not possible to obtain an acceptable analysis for this material, although TLC and spectra indicated that is was pure, it was recrystallized from ethyl acetate–cyclohexane to yield material of melting point 145–147 °C whose TLC behavior and spectral properties were identical with the 160–164.5 °C material: IR 3490, 1695, 1670, 1617 cm^{-1}; UV 241 nm (ϵ 14 500); NMR δ 5.75 (s, 1 H, C4-H), 3.50 (br s, 1 H, C20 H), 2.95 (vbr d, 1 H), 2.36 (s, 3 H, 1.17 (d, J = 6 Hz, 3 H), 1.09 (s, 3 H); MS, *m/e* (relative intensity) 342 (parent, 1.6), 326 (–H_2O, 17), 283 (–H_2O, C_2H_3O, 15), 161 (II, 100). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.46; H, 9.37.



II

(*Z*)-2′-[(Acetyloxy)methylene]-5′,17α-dihydro-5′α-methyl-2′*H*-18-nor-17α-androst-5-eno[13,17-*c*]furan-3β-ol (15). A solution of 264 mg (0.75 mmol) of **4** in 8 mL of glacial acetic acid was reacted with 500 mg of wet lead tetraacetate. After 4 h, 1 mL of glycerine was added and the mixture stirred for 45

min when it was diluted with distilled water. A crystalline precipitate formed slowly and after being filtered and dried yielded **15**: 224 mg (0.58 mmol, 77%); mp 163–165.5 °C (ethyl acetate–petroleum ether); IR 1755 cm^{-1}; UV 224 nm (ϵ 7300); NMR δ 6.68 (s, 1 H), 5.37 (m, 1 H, C6 H), 4.37 (q, 1 H, C20 H), 3.50 (m, 1 H, C3 H), 2.17 (s, 6 H), 1.33 (d, J = 6 Hz, 3 H, C21 H), 1.15 (s, 3 H, C19 H); MS, m/e (relative intensity) 386 (parent, 6), 344 ($-C_2H_2O$, 100), 326 ($-CH_3 - C_2H_2O$, 22). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.41; H, 8.82.

Formation of (*Z*)-2′-[(Acetyloxy)methylene]-5′,17α-dihydro-5′α-methyl-2′*H*-18-nor-17α-androst-5-eno[1,17-*c*]-furan-3β-ol Acetate (13) from the Enol Ether 7. A solution of 155 mg (0.43 mmol) of **7** in 5 mL of acetic acid was stirred magnetically and reacted with 500 mg of wet lead tetraacetate. After 1 h, 1 mL of glycerine was added to quench the excess lead tetraacetate and, after being stirred for 45 min, the solution was diluted to 25 mL to yield **13** which was filtered and washed with distilled water until neutral. Drying yielded **13**: 160 mg (0.39 mmol, 90%); mp 192–203 °C; IR 1740, 1730, 1685 (w), 1250, 1230 cm^{-1}; UV 224 nm (ϵ 7400); NMR δ 6.70 (s, 1 H, vinyl H geminal to acetoxy), 5.40 (m, 1 H, C6-H), 4.65 (br s, 1H, C3 H), 4.36 (q, J = 13, 6 Hz, 1 H, C20 H), 2.17 (s, 3 H), 2.03 (s, 3 H), 1.31 (d, J = 6.5 Hz, 3 H, C21 H), 1.13 (s, 3 H, C19 H); MS, m/e (relative intensity) 428 (parent, 6.7), 386 ($-C_2H_2O$, 99.5), 368 ($-C_2H_2O - C_2H_4O_2$, 100). Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.76; H, 8.73.

Formation of 13 from the Hydroxy Ketone 6. A solution of 170 mg (0.438 mmol) of **6** in 10 mL of glacial acetic acid was reacted with 500 mg of lead tetraacetate as above. After quenching with glycerine and dilution with dist water, 173 mg (0.404 mmol, 92%) of **13** was obtained.

(*Z*)-2′-[(Acetyloxy)methylene]-5′,17α-dihydro-5′α-methyl-2′*H*-18-nor-17α-androst-4-eno[13,17-*c*]furan-3-one (16). A solution of 364 mg (1.057 mmol) of **10** in 10 mL of glacial acetic acid was treated with 1 g of lead tetraacetate for 1 h when 1 mL of glycerine was added. After 45 min, the solution was diluted with distilled water to yield **16**: 308 mg (0.83 mmol, 79%); mp 166.5–172.5 °C; IR 1745, 1675, 1620 cm^{-1}; UV 237 nm (ϵ 20 500); NMR δ 6.70 (sharp s, 1 H, vinyl H geminal to acetoxy), 6.59 (s, 1 H, C4-H), 4.20 (q, J = 7 Hz, 1 H, C20 H), 2.20 (s, 3 H, OAc), 0.98 (d, J = 7 Hz, 3 H, C21 H), 0.97 (s, 3 H, C19 H); MS, m/e (relative intensity) 384 (parent, 3), 342 ($-C_2H_2O$, 100). Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.81, 74.58; H, 8.57, 8.32.

Hydrolysis of the Enol Ether 7 to the Hydroxy Ketone 6. To a solution of 22 mg (0.059 mmol) of **7** in 10 mL of tetrahydrofuran and 2 mL of water was added 22 mg of *p*-toluenesulfonic acid monohydrate. After 1 h, TLC on silica (1:9 and 1:4 ethyl acetate–benzene) indicated hydrolysis was complete. The volume of the solution was brought to 100 mL with distilled water from which 21 mg (0.054 mmol, 92%) of **6** slowly crystallized.

Hydrolysis of 16 to the Corticoid Side Chain in 2. Since **16** was unaffected by *p*-toluenesulfonic acid in tetrahydrofuran–water, it was hydrolyzed by using perchloric acid according to Wettstein.[11] To a solution of 196 mg (0.51 mmol) of **16** in 5 mL of tetrahydrofuran at room temperature was added 10 mL of 2.8 M per chloric acid. After 5 min, the solution was poured into water and the milky solution extracted twice with chloroform. The combined chloroform extracts were washed with dilute sodium bicarbonate, dried with sodium sulfate, and evaporated. The residue was taken up in ether and diluted with petroleum ether, and the ether was removed on a rotary evaporator under vacuum and without heat to yield, after filtering, **2**: 164 mg (0.41 mmol, 80%); mp 98–108 °C; IR 3440, 1755, 1675, 1620 cm^{-1}; UV 240 nm (ϵ 14 500); NMR δ 5.72 (s, 1 H, C4 H), 5.33 (d, J = 17.5 Hz, 1 H, C18-methylene H), 4.95 (d, J = 17.5 Hz, 1 H, C18-methylene H), 3.62 (m, 1 H, C20 H), 2.02 (s, 3 H, OAc), 1.18 (d, $J \simeq$ 6 Hz, 3 H, C21 H), 1.14 (s, 3 H, C19 H); MS, m/e (relative intensity) 384 (1, $-H_2O$), 342 (35, $-H_2O - CH_3CO$) 283 (22, $-COCH_2O_2CCH_3$), 43 (100). Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.35; H, 8.69.

Acetylation of 4. A 310-mg (0.84 mmol) sample of **4** was partially dissolved in 10 mL of chloroform, 1 mL of acetic anhydride, and 1.25 mL of pyridine and stirred at room temperature, protected from moisture. After 5 h, the solution was placed in a freezer overnight. The excess acetic anhydride was destroyed with methanol, and TLC indicated the presence of **6** and a little of the diacetate **5**. The volume was brought to 25 mL with methylene chloride, washed with distilled water, and extracted with dilute hydrochloric acid. The organics were dried with sodium sulfate, and TLC indicated that the majority of **6** had been converted to the enol ether **7**. The enol ether was hydrolyzed back to the hydroxy ketone **6** by *p*-toluenesulfonic acid in tetrahydrofuran–water. After dilution with water, the solids were collected, dried, and triturated with a small amount of ether to yield 175 mg (0.45 mmol, 54%) of **6**.

Preparation of 3β-Hydroxyandrost-5-ene-17-methanol Acetate (20). To a solution of 100 g of 21-acetoxypregnenolone[14] **17** in 2 L of tetrahydrofuran was added 20 g of lithium aluminum hydride. After the addition was complete, the solution was refluxed for 3 h, cooled to room temperature, and allowed to stand overnight. The excess $LiAlH_4$ was destroyed by slowly adding, in turn, 20 mL of water, 20 mL of 15% sodium hydroxide solution, and 20 mL of water. The mixture was filtered through filter aid to remove the precipitated salts. The solvent was removed under reduced pressure to yield 68 g of the known triol **18**.[15] The 68 g of triol **18** was dissolved in 1.4 L of tetrahydrofuran and cooled in an ice bath, and 68 g of sodium periodate dissolved in 600 mL of distilled water was added slowly. The mixture was stirred for 2 days and then filtered from the precipitated solids. The solids were washed with 2 L of water, followed by 2 L of methylene chloride. The solution was extracted twice with additional amounts of methylene chloride. The combined extracts were dried with magnesium sulfate and then evaporated. The residue was acetylated with a mixture of 250 mL of acetic anhydride and 400 mL of pyridine. After 2 h, TLC (5:95 methanol/chloroform) indicated the formation of the acetate, and the mixture was poured onto ice and water. The aldehyde[16] **19** crystallized, was filtered, and was dried: 40 g; IR 2720, 1725, 1255 cm^{-1}; NMR δ 9.78 (d, J = 1.5 Hz, 1 H), 5.40 (m, 1 H, C6), 4.61 (br s, 1 H, C3α H), 2.02 (s, 3 H), 1.03 (s, 3 H), 0.77 (s, 3 H).

The 40 g of aldehyde **19** was dissolved in 1 L of tetrahydrofuran, placed under nitrogen, and cooled to −5 °C. Then 60 g of lithium tri-*tert*-butoxyaluminum hydride was added as a slurry in THF during 0.75 h. The reaction mixture was stirred at −5 °C for 3 h and monitored by TLC (5:95 methanol/chloroform). The excess hydride was quenched by the additon of 95 mL of a saturated solution of sodium potassium tartrate (Rochelle salt) at −10 °C. The mixture was then stirred for an additional 4 h. The salts were filtered and washed thoroughly with additional tetrahydrofuran. The solvent was removed and the residue crystallized from ether/petroleum ether to yield **20**: 33 g; mp 159–163 °C (lit.[18] mp 157–158 °C); IR 3620 1735 cm^{-1}; NMR δ 5.38 (m, 1 H, C6), 4.72 (br s, 1 H, C3α H), 3.60 (br m, 2 H), 2.01 (s, 3 H), 1.02 (s, 3 H), 0.65 (s, 3 H). Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89. Found: C, 76.15; H, 10.13.

Barton Reaction on Alcohol 20. A solution of 4.0 g (11.54 mmol) of **20** in 50 mL of pyridine was cooled in an ice bath and then saturated with nitrosyl chloride. After 10 min, the solution was poured into water where it rapidly crystallized. After the mixture was stirred a few minutes, the precipitate was filtered, washed with water, and air-dried for 20 min. TLC (1:4 ethyl acetate/toluene) indicated a single compound. The nitrite was not characterized beyond recording its NMR spectrum: δ 5.33 (br s, C6 H), 4.63 (br d, 2 H, C20 H), 2.00 (s, 3 H), 1.02 (s, 3 H), 0.70 (s, 3 H). The nitrite ester **21** was dissolved in benzene, dried with sodium sulfate, and irradiated with a 450-W medium-pressure mercury arc (Pyrex filter) under argon for 0.5 h. TLC (1:1 ethyl acetate/toluene) indicated the presence of minor amounts of aldehyde **19** and alcohol **20** and a new major spot. Chromatography on silica yielded 1.143 g (3.04 mmol, 26%) of the 18-oxime **22** and 12% recovered starting material **20**. The oxime **22** possesses the following: mp 138–140 °C (acetone–water); IR 3400, 1740, 1720 (sh), 1275, 1260 cm^{-1}; NMR δ 7.33 (s, 1 H, oxime H), 5.34 (m, 1 H, C6), 4.58 (br s, 1 H, C3α H), 2.01 (s, 3 H, acetyl), 0.96 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ −34° (*c* 0.114%), $[\alpha]^{25}_{365}$ −69°. Anal. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.61; H, 8.89; N, 3.63.

Jones Oxidation of the Oxime 22. A solution of 256 mg (0.68 mmol) of oxime **22** in 50 mL of acetone was cooled in an ice bath and then oxidized with 0.5 mL of Jones reagent.[21] After 10 min, the excess oxidant was quenched with isopropyl alcohol and then

diluted with water to yield 120 mg (0.33 mmol, 49%) of the 18→20 lactone **23**.

Formation of the Lactone 23 by the Hypoiodite Reaction. A mechanically stirred solution of 4.0 g (11.4 mmol) of alcohol **20** in 400 mL of cyclohexane was heated to reflux, and, at reflux, the heating source was removed. To the hot solution were added 4.6 g of iodine and 18 g of lead tetraacetate, and the mixture was irradiated with a 500-W lamp. After 1 h, the initial lead tetraacetate charge appeared to be consumed, and an additional 10-g sample was added. The purple iodide color was discharged after a further 0.5 h of irradiation to yield a cream-colored suspension, which was filtered hot, using filter aid, to give a clear solution. The residue was washed with additional cyclohexane, and the combined organics were evaporated to yield an oil. The oil was taken up in 200 mL of acetone and oxidized at 0 °C with 6.5 mL of Jones reagent[21] for 0.5 h. The excess oxidant was quenched with isopropyl alcohol. After dilution with water, the mixture was extracted three times with methylene chloride, dried with sodium sulfate, and evaporated. The oily residue was taken up in ether and diluted with petroleum ether to yield 1.3 g of lactone **23**. A further 828 mg of lactone **23** was obtained by chromatography on silica by using 1:1 toluene/petroleum ether for a total yield of 2.13 g (5.87 mmol, 51%). Alternatively, the majority of lactone **23** could be obtained by crystallization from methanol, thus avoiding the chromatography. The yield by this method was 44–47%. The lactone **23** possesses the following: mp 168–170 °C; IR 1765, 1735, 1250 cm^{-1}; NMR δ 5.35 (br s, 1 H, C6 H), 4.60 (m, 1 H, C3α H), 4.35 (dd, J = 10.5 Hz, 1 H, C20α H), 4.06 (d, J = 10 Hz, 1 H, C20β H), 2.03 (s, 3 H, $COCH_3$), 1.10 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ −57.4° (c 0.108%), $[\alpha]^{25}_{365}$ −187°. Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.67; H, 8.56.

3β-Hydroxy-17-(hydroxymethyl)androst-5-en-18-oic Acid γ-Lactone (24). The lactone **23** (9.80 g, 27.3 mmol) was suspended in 0.5 L of methanol and stirred magnetically. To this was added 19 g of potassium carbonate in 100 mL of distilled water. After 1.75 h, TLC (1:1 or 1:4 ethyl acetate/toluene) indicated complete consumption of **23**. The majority of the methanol was removed on a rotary evaporator and then diluted to 0.5 L with water. The resultant precipitate was filtered, washed with distilled water, and dried to give lactone **24**: 8.05 g (25.4 mmol, 93%); mp 191–192.5 °C; IR 3510, 1755, 1745 cm^{-1} (split carbonyl); NMR δ 5.31 (br s, 1 H, C6), 4.37 (dd, J = 10.5 Hz, 1 H, C20α H), 4.05 (d, J = 10 Hz, 1 H, C20β H), 3.50 (br s, 1 H, C17α H), 1.10 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ −228° (c 0.108%), $[\alpha]^{25}_{365}$ −50°. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.70; H, 8.93.

3-Oxo-17β-(hydroxymethyl)androst-4-en-18-oic Acid γ-Lactone (25). The hydroxy lactone **24** (7.80 g, 24.7 mmol) was dissolved in 800 mL of toluene and 48 mL of *N*-methyl-4-piperidone, brought to reflux, and dried by using a Dean–Stark trap. The dried solution was cooled slightly and 16 g of aluminum isopropoxide added. After being placed under argon, the reaction mixture was refluxed for 18 h. After cooling, the mixture was transferred into a seperatory funnel and washed three times with a total of 300 mL of concentrated hydrochloric acid in 1800 mL of water. The resulting solution was washed with 1 L of distilled water and dried with sodium sulfate. The toluene was reduced to a small volume, whence the enone started to crystallize. The volume was brought to 150 mL with petroleum ether, and the crystals were filtered to yield enone **25**: 6.05 g, 19.3 mmol (78%); 228.5–229.5 °C (ethyl acetate/petroleum ether); IR 1760 (sh), 1750, 1670, 1617 cm^{-1}; UV 240 nm (ϵ 16 000); NMR δ 5.72 (s, 1 H, C4, 4.35 (dd, J = 10.5 Hz, C20α H), 4.09 (d, J = 10 Hz, 1 H, C20β H), 1.27 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ +91° (c 0.098%), $[\alpha]^{25}_{365}$ −8°. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.41; H, 8.42.

3-Ethylene Ketal of Enone 25. The enone **25** (6.05 g, 19.3 mmol) was suspended in 650 mL of ethylene glycol containing 200 mg of *p*-toluenesulfonic acid.[25] The mixture was distilled at 55 °C (0.5 mm) until approximately 450 mL of distillate had accumulated. After the mixture cooled, the vacuum was broken and 2 mL of pyridine added to the distillation residue. The mixture was then diluted to 0.5 L with distilled water. The resultant precipitate was filtered and dried to give intermediate **26**: 6.20 g (17.3 mmol, 90%); mp 195–205 °C; IR 1765 cm^{-1}; NMR δ 5.31 (m, 1 H, C6), 4.32 (dd, J = 10.5 Hz, 1 H, C20α H), 4.05 (d, J = 10 Hz, 1 H, C20β H), 3.93 (s, 4 H), 1.11 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ −31° (c 0.105%), $[\alpha]^{25}_{365}$ −122°. Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.43. Found: C, 72.62; H, 8.39.

3-Ethylene Ketal of 17β-(Hydroxymethyl)-13β-acetyl-18-norandrost-5-en-3-one (27). To a suspension of 5.50 g (15.34 mmol) of lactone ketal **26** in 0.5 L of dry ether under argon was added, via syringe, 50 mL of 1.6 M methyllithium in ether. The vigor of the reaction caused the ether to boil. The resultant suspension was refluxed 0.75 h to complete the reaction. The excess methyllithium was destroyed by the careful addition of water through an addition funnel. After quenching, additional water was added and the ether layer seperated. After the mixture was dried with sodium sulfate, the solvent was removed, and residue was flash chromatographed[34] with 15:85 ethyl acetate/methylene chloride to yield **27**: 4.20 g (11.22 mmol 73%); mp 164–168 °C (ether/petroleum ether); IR 3420, 1705, 1695 cm^{-1}; NMR δ 5.30 (m, 1 H, C6), 3.42 (s, 4 H), 3.04 (d, $J \simeq$ 8 Hz, 2 H, resolved AB for C20 H), 2.21 (s, 3 H, $COCH_3$), 0.91 (s, 3 H); $[\alpha]^{25}_{589}$ −35° (c 0.129%), $[\alpha]^{25}_{365}$ −122°. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.88; H, 9.33.

The acetate **28** was prepared by dissolving 202 mg (0.54 mmol) of ketal **27** in 5 mL of methylene chloride and adding 0.8 mL of acetic anhydride and 1.0 mL of pyridine plus a few crystals of 4-(dimethylamino)pyridine.[35] After 2 h, the methylene chloride was removed and methanol added. The resultant solution was slowly diluted with water to yield acetate **28**: 206 mg (0.50 mmol, 93%); mp 147–150.5 °C; IR 1740, 1700 cm^{-1}; NMR δ 5.32 (m, 1 H, C6 H), 5.05 (m, 2 H), 4.93 (s, 4 H), 2.15 (s, 3 H), 2.06 (s, 3 H), 0.92 (s, 3 H); $[\alpha]^{25}_{589}$ −46° (c 0.103%), $[\alpha]^{25}_{365}$ −177°. Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.09; H, 8.71. Found: C, 72.35; H, 8.36.

17β-(Hydroxymethyl)-13β-acetyl-18-norandrost-4-en-3-one (29). To a solution of 3.50 g (9.35 mmol) of ketal **27** in 250 mL of acetone was added 1 g of *p*-toluenesulfonic acid in 50 mL of water, and the resultant solution was refluxed for 1 h. The majority of the acetone was evaporated to give an oil which rapidly crystallized. After dilution with water, the enone **29** was filtered and dried: 3.00 g (9.08 mmol, 97%); 143–148 °C; IR 3420, 1700, 1675, 1615 cm^{-1}; UV 240 nm (ϵ 16 250); NMR δ 5.71 (s, 1 H, C4), 3.08 (br s, 2 H, C20 H), 2.25 (s, 3 H), 1.08 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ +115° (C 0.122%), $[\alpha]^{25}_{365}$ +113°. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.23; H, 9.46.

The acetate **30** was formed from the alcohol **29** by dissolving it in 5 mL of methylene chloride and adding 0.8 mL of acetic anhydride and 1 mL of pyridine plus a few crystals of 4-(dimethylamino)pyridine. After 1.75 h, the methylene chloride was removed, and the mixture was diluted with methanol and then water to yield **30**: 148 mg (0.40 mmol, 65%); mp 98–100 °C; IR 1745, 1700, 1680, 1620 cm^{-1}; UV 240 nm (ϵ 16 500); NMR δ 5.72 (s, 1 H, C4), 4.02 (m, 2 H), 2.19 (s, 3 H), 2.08 (s, 3 H), 1.11 (s, 3 H); $[\alpha]^{25}_{589}$ +77° (C 0.100%), $[\alpha]^{25}_{365}$ +35°. Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.76; H, 8.65.

Alternatively, **30** can be prepared from the ketal acetate **28** by using the same conditions which were used for **27**.

Reaction of the Hydroxy Ketone 29 with Lead Tetraacetate. To a magnetically stirred solution of 1.70 g (5.14 mmol) of **29** in 60 mL of glacial acetic acid was added 2.5 g of wet lead tetraacetate. After 1 h, excess oxidant was quenched with 5 mL of glycerine, and, after 1 h, the reaction mixture was diluted with water to yield, acetoxylated enol ether **31** 1.74 g (4.70 mmol, 92%): mp 201–208 °C; IR 1745, 1675, 1620 cm^{-1}; UV 237 nm (ϵ 22 850); NMR δ 6.69 (s, 1 H), 5.73 (br s, 1 H, C4), 4.13 (m, 2 H, not well resolved AB quartet), 2.18 (s, 3 H), 1.28 (s, 3 H); $[\alpha]^{25}_{589}$ +80° (c 0.161%), $[\alpha]^{25}_{365}$ +21°. Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.30; H, 8.23.

13β-(Acetoxyacetyl)-17β-(hydroxymethylene)-18-norandrost-4-en-3-one (32). To a magnetically stirred solution of 2.80 g (7.56 mmol) of enol **31** in 70 mL of THF was added 140 mL of 2.8 M aqueous perchloric acid.[13] After being stirred for 10 min, the solution was further diluted and then extracted three times with methylene chloride. The combined organics were washed with 3% aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated. The residue was crystallized from ether to yield switched 18-hydroxydeoxycorticosterone acetate **32**: 2.00

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g (5.15 mmol, 68%); mp 136–139 °C; IR 3430, 1755, 1715, 1665, 1620 cm^{-1}; UV 240 nm (ϵ 17 250); NMR δ 5.70 (s, 1 H, C4 H), 5.03 (s, 2 H, OCH_2CO), 3.70 (br m, 2 H), 2.70 (s, 3 H), 1.14 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ +122° (c 0.103%), $[\alpha]^{25}_{365}$ +86°. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.22; H, 8.41.

13β-(Hydroxyacetyl)-17β-(hydroxymethylene)-18-norandrost-4-en-3-one (33). To a magnetically stirred solution of 1.00 g (2.57 mmol) of the acetate **32** in 90 mL of methanol was added a solution of 2.25 g of potassium bicarbonate in 9 mL of distilled water.[28] After 3 h TLC (EtOAc) indicated complete hydrolysis of the acetate, the bulk of the methanol was removed, and the residue was diluted with distilled water. The oil which separated was extracted with methylene chloride. The extracts were dried with sodium sulfate and evaporated to an oil which was flash chromatographed by using 1:1 ethyl acetate/methylene chloride. The appropriate fractions were combined and evaporated to an oil which was dissolved in a little ethyl acetate and filtered. The filtrate was concentrated to dryness and the residue crystallized from 10 mL of ether which after the majority of crystallization had occurred was further diluted with 10 mL of petroleum ether to yield 479 mg (1.39 mmol, 54%) of the 13,17-switched isomer of 18-hydroxydeoxycorticosterone **33** (mp 73–143 °C); a similar melting point range was observed for several different samples of **33**. Probably a chemical reaction was occurring between the hydroxymethylene and hydroxyacetyl groups upon heating, but this point was not investigated: IR 3440, 1700, 1675, 1620 cm^{-1}; UV 240 nm (ϵ 15 250); NMR δ 5.71 (s, 1 H, C4), 4.67 (dd, J = 18, 5 Hz, 1 H), 4.18 (dd, J = 18, 5 Hz, 1 H), 3.50 (m, 2 H), 1.07 (s, 3 H); $[\alpha]^{25}_{589}$ +116° (c 0.100%), $[\alpha]^{25}_{365}$ +78°. Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.35; H, 8.95.

13β-(Acetoxyacetyl)-17β-formyl-18-norandrost-4-en-3-one (34). To a magnetically stirred solution of 313 mg (0.80 mmol) of alcohol **32** in 20 mL of methylene chloride, buffered with 98 mg (1.2 mmol) of sodium acetate, was added 259 mg (1.2 mmol) of pyridinium chlorochromate.[33] After 3 h ether was added and the mixture filtered through filter aid. The residue was washed with additional ether, and then the combined organics were stripped to an oil. The oil was flash chromatographed by using 1:1 ethyl acetate/methylene chloride. The appropriate fractions were combined and crystallized from ether/petroleum ether to yield the 13,17-switched isomer of 18-oxodeoxycorticosterone acetate (**34**): 154 mg (0.40 mmol, 50%); mp 63–100 °C, bubbled 110–132 °C; IR 1755, 1725, 1675, 1620 cm^{-1}; UV 240 nm (ϵ 16 000); NMR δ 9.72 (d, J = 3 Hz, 1 H), 5.72 (s, 1 H, C4), 4.98 (d, J = 17 Hz, AB q, 1 H), 4.63 (d, J = 17 Hz, AB q, 1 H), 2.18 (s, 3 H), 1.16 (s, 3 H, C19); $[\alpha]^{25}_{589}$ +90° (C 0.100%), $[\alpha]^{25}_{365}$ −54°. Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.37; H, 7.80.

13β-Acetyl-17β-formyl-18-norandrost-4-en-3-one (35). To a magnetically stirred solution of 507 mg (1.53 mmol) of **29** in 40 mL of methylene chloride were added 494 mg of pyridinium chlorochromate and 189 mg of sodium acetate. After being stirred at room temperature for 4 h, the dark mixture was filtered through filter aid which was, in turn, washed with additional ether. The residue, after evaporation, was flash chromatographed with 4:6 ethyl acetate/methylene chloride to give 450 mg of crystalline residue. Recrystallization from ether–petroleum ether gave a 9:1 mixture of 17β to 17α epimers. The 17α epimer has NMR resonances at δ 9.67 (aldehyde) and 2.10 (acetyl methyl). Pure 17β epimer **35** was obtained by recrystallization from ether containing a little methanol: mp 152–174 °C; IR 2730, 1725, 1710, 1670, 1617 cm^{-1}; UV 240 nm (ϵ 16 300); NMR δ 9.73 (d, J = 3 Hz, 1 H), 5.70 (s, 1 H), 2.23 (s, 3 H), 1.07 (s, 3 H); $[\alpha]^{25}_{589}$ +3.0° (c 1.05%, $CHCl_3$), $[\alpha]^{25}_{365}$ −95.2°. Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.47; H, 8.64.

13β-Acetyl-17β-(hydroxymethylene)-18-norandrost-5-en-3β-ol (36). To a solution of 2.00 g (5.58 mmol) of lactone **23** in 0.5 L of dry ether, under argon, was added 50 mL of 1.6 M methyllithium in ether via syringe. There was an immediate white precipitate. For completion of the reaction, the mixture was refluxed for 2 h and then cooled. The excess methyllithium was destroyed by careful additon of 5 mL of water in 50 mL of tetrahydrofuran. After the initial vigorous reaction was over, the mixture was further diluted with 400 mL of water. The ether layer was separated, dried with sodium sulfate, and evaporated. The white solid was recrystallized from methylene chloride/ethyl acetate with further dilution with petroleum ether to yield **36**: 1.40 g (3.91 mmol, 70%); mp 162.5–166 °C; IR 3430 1700, 1690 (sh) cm^{-1}; NMR δ 5.34 (br s, 1 H, C6), 3.58 (m, 3 H, C3, 20 H), 2.23 (s, 3 H), 0.91 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ −52° (c 0.103%), $[\alpha]^{25}_{365}$ −197°. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.74; H, 9.84.

Lead Tetraacetate Acetoxylation of the Hydroxy Acetyl Compound 36. To a solution of 600 mg (1.80 mmol) of compound **36** in 20 mL of glacial acetic acid was added 1.2 g of wet lead tetraacetate. After 1 h, excess oxidant was quenched with 1.5 mL of glycerine and after a further 0.25 h, the mixture was diluted with water. The resultant gum was extracted with methylene chloride, and the extracts were washed with dilute sodium bicarbonate and dried with sodium sulfate. The residue after evaporation was flash chromatographed with 1:4 ethyl acetate/methylene chloride. The appropriate fractions were combined, evaporated, and crystallized from 25 mL of 1:2 ether/petroleum ether to yield, the acetoxylated enol ether **37**: 473 mg (1.27 mmol, 72%); mp 95–100 °C dec; IR (chloroform) 3620, 1750, 1695, 1250 cm^{-1}; UV 220 nm (end, ϵ 7500); NMR δ 6.67 (s, 1 H), 5.32 (br s, 1 H, C6 H), 4.08 (m, 2 H, C20 H), 3.50 (br s, C3 H), 2.17 (s, 3 H), 1.12 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ −7.8° (c 0.102%), $[\alpha]^{25}_{365}$ −4.9°. Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.15; H, 8.96.

13-(Acetoxyacetyl)-17β-(hydroxymethylene)-18-norandrost-5-en-3β-ol (38). Compound **36** (400 mg, 1.20 mmol) was treated with lead tetraacetate to produce **37**. Crude **37** was dissolved in 10 mL of tetrahydrofuran and 20 mL of 2.8 M perchloric acid added. After 10 min, the solution was poured into water and extracted twice with methylene chloride. The organics were washed with dilute sodium bicarbonate, treated with decolorizing carbon, filtered through filter aid, and evaporated. The resultant oil was dissolved in ether whence crystallization commenced and yielded **38**: 285 mg (0.73 mmol, 61%); mp 159.5–164 °C; IR 3490, 1750, 1710 cm^{-1}; NMR δ 5.30 (br s, 1 H, C6), 5.14 (d, J = 18 Hz, AB q, 1 H), 4.84 (d, J = 18 Hz, AB q, 1 H), 3.50 (m, 3 H, C3α,20 H), 2.17 (s, 3 H), 0.94 (s, 3 H, C19 H); $[\alpha]^{25}_{589}$ −34° (c 0.142%), $[\alpha]^{25}_{365}$ −71°. Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.45; H, 9.12.

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